In the Specification:

Please replace the paragraph beginning at page 1, line 10 with the following rewritten paragraph:

--This application is a division of United States Application Serial No. 08/196,082, filed March 3, 1994, now abandoned, which is a continuation of International Application No. PCT/US92/07381, filed August 28, 1992; and a continuation-in-part of United States Patent Application Serial No. 08/182,117, filed January 27, 1994, now abandoned, which is a continuation-in-part of International Application No. PCT/US92/06283, filed July 30, 1992, United States Patent Application Serial No. 07/750,579, filed August 28, 1991, now abandoned, and United States Patent Application Serial No. 07/738,040, filed July 30, 1991; now abandoned, which is a continuation-in part of United States Patent Application Serial No. 07/559,955, filed July 31, 1990, now abandoned, which is a continuation-in-part of United States Patent Application Serial No. 07/472,070, filed January 30, 1990, now abandoned, which is a continuation-in-part of United States Patent Application Serial No. 07/388,044, filed July 31, 1989, now abandoned.--

Please replace the paragraph beginning at page 12, line 17 with the following rewritten paragraph:

--Figure 6. Nucleotide sequence of human TPO gene after site-directed mutagenesis (SEQ ID NO: 1). The mutations incorporated two stop codons, as well as an EcoR1site for confirmation, in the region immediately upstream from the transmembrane region of the human TPO gene.--

Please replace the paragraph beginning at page 12, line 22 with the following rewritten paragraph:

--Figure 7. cDNA sequence (SEQ ID NO: 2) and derived amino acid sequence (SEQ ID NO: 3) of human thyroid peroxidase (Magnusson, R.P., et al., Mol. Endocrinol. 1:856-861 (1987)). FIG. 7A depicts the cDNA sequence of human thyroid peroxidase from nucleotides 1 to 486, and the amino acid sequence of human thyroid peroxidase from amino acids 1 to 134. FIG. 7B depicts the cDNA sequence of human thyroid peroxidase from nucleotides 487 to 972, and the amino acid sequence of

human thyroid peroxidase from amino acids 135 to 296. FIG. 7C depicts the cDNA sequence of human thyroid peroxidase from nucleotides 973 to 1458, and the amino acid sequence of human thyroid peroxidase from amino acids 297 to 458. FIG. 7D depicts the cDNA sequence of human thyroid peroxidase from nucleotides 1459 to 1945, and the amino acid sequence of human thyroid peroxidase from amino acids 459 to 620. FIG. 7E depicts the cDNA sequence of human thyroid peroxidase from nucleotides 1946 to 2484, and the amino acid sequence of human thyroid peroxidase from amino acids 621 to 800. FIG. 7F depicts the cDNA sequence of human thyroid peroxidase from nucleotides 2485 to 3072, and the amino acid sequence of human thyroid peroxidase from amino acids 801 to 933. Asterisks (*) indicate potential glycosylation sites. The carets (^^^) at nucleotides 2884, 2885, and 2886 indicate an in phase termination codon. The carets (^^^ ^^^) at nucleotides 3042 to 3048 indicate a polyadenylation signal near the 3'-end.--

Please replace the paragraph beginning at page 15, line 14 with the following rewritten paragraph:

--Figure 18. Determination of the epitope for the anti-microsomal/TPO monoclonal antibody 20.10. The nucleotide sequences of the 5' - and 3'-ends were determined for 14 clones selected from the hTPO cDNA fragment library. These boundaries are annotated by the numbers assigned to the nucleotides in hTPO previously reported (Magnusson, R.P., et al., Mol. Endocrinol. 1:856-861 (1987)). The smallest region of overlap between all 14 clones is from 881-927 b.p. The first two nucleotides in this span do not constitute a complete codon, so the epitope area can be defined as between 883-927 b.p. (SEQ ID NO: 4), corresponding to the derived amino acid sequence shown (SEQ ID NO: 5).--

Please replace the paragraph beginning at page 15, line 26 with the following rewritten paragraph:

--Figure 19. Determination of the epitope recognized by TPO Mab 47. The nucleotide sequences of the 5'- and 3'-prime ends were determined for 18 clones in the TPO cDNA fragment library (see Material and Methods) recognized by Mab 47. The smallest region of overlap between all 18

clones is from 2219-2247 (SEQ ID NO: 6) basepairs in the human TPO cDNA sequence, coding for the indicated amino acids (SEQ ID NO: 7).--

Please replace the paragraph beginning at page 16, line 13 with the following rewritten paragraphs:

--Figure 21: Binding affinity of Fab fragment SP2 for recombinant human thyroid peroxidase (TPO). Brackets indicate the mean ± the range of duplicate densitometric values obtained for each TPO concentration in a representative experiment. Comparable results were obtained in two additional experiments.

Figures 22A to 22B: Fig.22A. Effect of increasing molar (M) concentrations of TPO, lactoperoxidase (LPO) or myeloperoxidase (MPO) on the binding of ^{125} I-TPO by SP1.2. Background binding in the absence of Fab fragments (~2%) was subtracted. Fig.22B. Competition inhibition by unlabeled TPO of radiolabeled TPO binding to the Fab fragments. In the absence of unlabeled TPO, binding values for the three Fab fragments were 13-15%. Background of ~2% was subtracted. Dissociation constants (Kd) were determined by Scatchard analysis (Scatchard, G., "The attractions of proteins for small molecules and ions," Ann. NY Acad. Sci. VOL 51:660-672 (1949)) and are:

SP2 =8.3×10^{-11}M ; SP4 = 2.2×10^{-10}M; SP5 = 3×10^{-11}M

Figure 23: Inhibition by increasing molar (M) concentrations of SP1.2 on the binding to ^{125}I-TPO by serum TPO autoantibodies. The mean values (± S.E.M.) obtained for sera from 11 patients are shown by solid circles. Background binding by serum from a TPO autoantibody negative donor was not subtracted and is shown by the open circles (mean ± S.E.M. of 3 experiments).

Figures 24A to 24C: Competition ELISA for binding to TPO between the SP1.2 Fab fragment and TPO autoantibodies of different IgG subclasses. Figs. 24A to 24C show data obtained with three different patients. TPO autoantibody levels are shown as the 0.D. readings measured at 492nm.

Background O.D. values obtained for TPO autoantibody-negative serum were <0.05. SP1.2 (M); molar concentration of SP1.2.

Figures 25A to 25B: Effect of denaturation of TPO on SP Fab fragment binding. Binding of SP1.2, SP1.4 and SP1.5 Fig. 25A or mouse monoclonal antibody #40.28 Fig. 25A was measured to native or denatured TPO by ELISA. Binding is shown as the O.D. value at 492nm. Background O.D. values for TPO autoantibody negative serum and control murine ascites were <0.05.

Figure 26: Binding domains on TPO for the SP1.2, SP4.6, SP1.20 F(ab)s. ^{125} I-TPO was preincubated in the absence or presence of increasing concentrations of SP4.6, SP1.20 or SP1.2 [Free F(ab)]. The ability of these complexes to bind to immobilized SP1.2 was then determined. The results are expressed as % ^{125}I-TPO bound after subtraction of background values (~ 2%) obtained using buffer alone.

Figures 27A to 27D: Domains on TPO recognized by F(ab)s. Increasing concentrations of one F(ab) were pre-incubated with radiolabeled TPO and then added to a second, immobilized F(ab) (Methods). The immobilized F(ab) was TRI.9 Fig. 27A, TR1.7 Fig 27C and SP1.5 Fig 27D. The ability of the free F(ab) to inhibit binding to itself is shown by the open circles. Confirmation of the binding potency of the free F(ab)s was determined concurrently in each experiment. A representative control Fig. 27B for the experiment in Fig. 27A. is shown.

Figure 28: Schematic representation of the binding domains on TPO for the expressed F(ab)s.

Figures 29A to 29C: Domains on TPO recognized by autoantibodies in 3 representative sera Figs. 29A ,29B and 29C from patients with autoimmune thyroid disease. F(ab)s WR1.7 and TR1.9, alone or in combination, were used to compete for serum autoantibody binding to radiolabeled TPO (Methods).--

Please replace the paragraph beginning at page 48, line 21 with the following rewritten paragraph:

--The non-coding strand of human TPO cDNA, in the phagemid Bluescript (Stratagene, San Diego, CA), was used as a template for oligonucleotide-directed mutagenesis. A 52 bp mutagenic primer (5' -AGGCTCCCTCGGGTGACTTGAATTCCCATGTAGCTGGCTGCTCTGCTGATCG-3'), (SEQ ID NO: 8) synthesized by the molecular Genetics Core Facility, San Francisco Veterans' Administration Medical Center, was designed to generate two stop codons directly upstream of the putative membrane-spanning region of the protein. Thus, TGA and TAG codons were created at 2629-2631 bp and 2641-2643 bp in human TPO cDNA (Magnusson, R.P., et al., Mol. Endocrinol. 1:856-861 (1987)), respectively. The cDNA sequence of human TPO as published on page 857 as Fig. 2 in Magnusson, R.P., et al., Mol. Endocrinol. 1:856-861 (1987) is as follows:

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gaggcaattgaggcgcccatttcagaagagttacagccgtgaaaattactcagcagtgca  60
gttggctgagaagaggaaaaaagaatgagagcgctggctgtgctgtctgtcacgctggtt 120
atggcctgcacagaagccttcttccccttcatctcgagagggaaagaactcctttgggga 180
aagcctgaggagtctcgtgtctctagcgtcttggaggaaagcaagcgcctggtggacacc 240
gccatgtacgccacgatgcagagaaacctcaagaaaagaggaatcctttctggagctcag 300
cttctgtctttttccaaacttcctgagccaacaagcggagtgattgcccgagcagcagag 360
ataatggaaacatcaatacaagcgatgaaaagaaaagtcaacctgaaaactcaacaatca 420
cagcatccaacggatgctttatcagaagatctgctgagcatcattgcaaacatgtctgga 480
tgtctcccttacatgctgcccccaaaatgcccaaacacttgcctggcgaacaaatacagg 540
cccatcacaggagcttgcaacaacagagaccaccccagatggggcgcctccaacacggcc 600
ctggcacgatggctccctccagtctatgaggacggcttcagtcagccccgaggctggaac 660
cccggcttcttgtacaacgggttcccactgcccccggtccgggaggtgacaagacatgtc 720
attcaagtttcaaatgaggttgtcacagatgatgaccgctattctgacctcctgatggca 780
tggggacaatacatcgaccacgacatcgcgttcacaccacagagcaccagcaaagctgcc 840
ttcgggggagggtctgactgccagatgacttgtgagaaccaaaacccatgttttcccata 900
caactcccggaggaggcccggccggccgcgggcaccgcctgtctgcccttctaccgctct 960
tcggccgcctgcggcaccggggaccaaggcgcgctctttgggaacctgtccacggccaac 1020
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ccgaggcagcagatgaacgggttgacctcgttcctggacgcgtccaccgtgtatggcagc 1080
tccccggccctagagaggcagctgcggaactggaccagtgccgaagggctgctccgcgtc 1140
cacggccgcctccgggactccggccgcgcctacctgcccttcgtgccgccacgcgcgcct 1200
gcggcctgtgcgcccgagcccggcaaccccggagagacccgcgggccctgcttcctggcc 1260
ggagacggccgcgccagcgaggtcccctccctgacggcactgcacacgctgtggctgcgc 1320
gagcacaaccgcctggccgcggcgctcaaggccctcaatgcgcactggagcgcggacgcc 1380
gtgtaccaggaggcgcgcaaggtcgtgggcgctctgcaccagatcatcaccctgagggat 1440
tacatccccaggatcctgggacccgaggccttccagcagtacgtgggtccctatgaaggc 1500
tatgactccaccgccaaccccactgtgtccaacgtgttctccacagccgccttccgcttc 1560
ggccatgccacgatccacccgctggtgaggaggctggacgccagcttccaggagcacccc 1620
gacctgcccgggctgtggctgcaccaggctttcttcagcccatggacattactccgtgga 1680
ggtggtttggacccactaatacgaggccttcttgcaagaccagccaaactgcaggtgcag 1740
gatcagctgatgaacgaggagctgacggaaaggctctttgtgctgtccaattccagcacc 1800
ttggatctggcgtccatcaacctgcagaggggccgggaccacgggctgccaggttacaat 1860
gagtggagggagttctgcggcctgcctcgcctggagacccccgctgacctgagcacagcc 1920
atcgccagcaggagcgtggccgacaagatcctggacttgtacaagcatcctgacaacatc 1980
gatgtctggctgggaggcttagctgaaaacttcctccccagggctcggacagggcccctg 2040
tttgcctgtctcattgggaagcagatgaaggctctgcgggacggtgactggttttggtgg 2100
gagaacagccacgtcttcacggatgcacagaggcgtgagctggagaagcactccctgtct 2160
cgggtcatctgtgacaacactggcctcaccagggtgcccatggatgccttccaagtcggc 2220
aaattccccgaagactttgagtcttgtgacagcatcactggcatgaacctggaggcctgg 2280
agggaaacctttcctcaagacgacaagtgtggcttcccagagagcgtggagaatggggac 2340
tttgtgcactgtgaggagtctgggaggcgcgtgctggtgtattcctgccggcacgggtat 2400
gagctccaaggccgggagcagctcacttgcacccaggaaggatgggatttccagcctccc 2460
ctctgcaaagatgtgaacgagtgtgcagacggtgcccacccccctgccacgcctctgcg 2520
aggtgcagaaacaccaaaggcggcttccagtgtctctgcgcggacccctacgagttagga 2580
gacgatgggagaacctgcgtagactccgggaggctccctcgggtgacttggatctccatg 2640
tcgctggctgctctgctgatcggaggcttcgcaggtctcacctcgacggtgatttgcagg 2700
tggacacgcactggcactaaatccacactgcccatctcggagacaggcggaggaactccc 2760

gagctgagatgcggaaagcaccaggccgtagggacctcaccgcagcgggccgcagctcag 2820
gactcggagcaggagagtgctgggatggaaggccgggatactcacaggctgccgagagcc 2880
ctctgagggcaaagtggcaggacactgcagaacagcttcatgttcccaaaatcaccgtac 2940
gactcttttccaaacacaggcaaatcggaaatcagcaggacgactgttttcccaacacgg 3000
gtaaatctagtaccatgtcgtagttactctcaggcatggatgaataaatgttatagctgc 3060
aaaaaaaaaaaa 3072 (SEQ ID NO: 2).

For convenient screening of mutants, an Eco RI restriction site (GAATTC, at 2630-2635 bp) was created together with the first (TGA) stop codon. The mutagenesis procedure was performed according to the protocol of the manufacturer (Muta-gene phagemid in vitro mutagenesis kit, Biorad, Richmond, CA) to generate the plasmid pHTPO(M1)-BS.--

Please replace the paragraph beginning at page 69, line 2 with the following rewritten paragraph:

--TPO cDNA fragment library construction: A full-length (3.05 kb) cDNA clone as described above for human thyroid peroxidase was released from its Bluescript vector (Stratagene, San Diego, CA.) by digestion with EcoRI (BRL Laboratories, Gaithersburg, MD) and NotI (Boehringer, Mannheim, West Germany). Because both vector and insert are of similar length, the Bluescript was further digested with ScaI (New England Biolabs, Beverly, MA.). The TPO cDNA was purified by agarose gel electrophoresis and electroelution. The cDNA was then digested (6 minutes at room temperature) into small random-sized fragments with DNAase I (0.1 ng DNase/ug cDNA) (BRL) in 20 mM Tris-HCl, pH 7.5, 1.5 mM $MnCl_2$ and bovine serum albumin, 100 ug/ml. After electrophoresis in 2% SeaPlaque agarose (FMC Bio Products, Rockland, ME), TPO cDNA fragments 200-500 b.p. in length were recovered by electroelution. The ends of the fragments were blunted with the Klenow fragment of DNA polymerase I, and ligated to EcoRI linkers (GAATTCGGCACGAG) (SEQ ID NO: 9) containing a nonphosphorylated EcoRI cohesive end and a phosphorylated blunt end (Pharmacia, Piscataway, NJ). After phosphorylation with polynucleotide kinase, excess linkers were removed by electrophoresis in 2% SeaPlaque agarose. The linker-ligated cDNA was again size-selected (200-500 b.p.), electroeluted, ethanol precipitated

and ligated into EcoRI-cut lambda-Zap vector (Stratagene). After packaging (Giga-Pak Gold, Stratagene), the library was amplified in XL1-blue cells (Stratagene). cDNA insert sizes were confirmed by the polymerase chain reaction (PCR) (Saiki, R.K., et al., Science 239:487-491 (1988)) using the Bluescript reverse and -20 primers. PCR analysis of the "C2" hTPO cDNA region (Libert, F., et al., EMBO J. 6:4193-4196 (1987); Ludgate, M., et al., J. Clin. Endocrinol. Metab. 68:1091-1096 (1989)) in the TPO cDNA fragment library was performed using two oligonucleotide 22-mer primers (5'- GGTTACAATGAGTGGAGGGAGT (SEQ ID NO: 10) and 5' - GTGGCTGTTCTCCCACCAAAAC) (SEQ ID NO: 11) spanning the region 1852 -2112 b.p. in hTPO (17). PCR (30 cycles) was for 1 minute at 94°C, 2 minutes at 55°C and 1 minute at 72°C. For screening the library, the PCR-generated DNA was labeled with ^{32}P-αCTP to a specific radioactivity of 0.8 x 10^9 cpm/ug DNA using the random primer method (Multiprime; Amersham, Arlington Heights, IL). The screening procedure employed standard techniques (Maniatis, T., et al., Molecular Biology: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1982)), with final washes of 30 minutes (x 2) at 55°C in 0.1 x SSC, 1% SDS buffer (1 x SSC in 150 NaCl, 15 mM Na citrate, pH 7.5). Autoradiography of the nitrocellulose filters was performed with Kodak XAR-5 film.--

Please replace the paragraph beginning at page 73, line 21 with the following rewritten paragraph:

--Screening of this library with the anti-microsomal antigen monoclonal antibody yielded 6-12 positive plaques per 1,000 plaques screened. Fourteen positive clones were randomly chosen for partial nucleotide sequencing to delineate the position of their TPO cDNA inserts relative to the entire TPO gene. Twelve of the 14 clones had cDNA inserts of 160-350 b.p. Two clones (U and Y) that had cDNA inserts slightly larger than the expected 500 b.p. maximum were found, upon nucleotide sequencing, to have double cDNA inserts. As an indication of the success of the procedure, all 14 clones recognized by the monoclonal antibody spanned the same region (746-1,150 b.p.) of the hTPO gene (Magnusson, R.P., et al., Mol. Endocrinol. 1:856-861 (1987)) (Figure 18). The maximum region common to all clones, and therefore an indication of a common epitope, was between bases 881 and 927 (AA AAC CCA TGT TTT CCC ATA CAA CTC CCG

GAG GAG GCC CGG CCG GCC) (SEQ ID NO: 12), corresponding to a derived amino acid sequence of only 15 residues (Asn Pro Cys Phe Pro Ile Gln Leu Pro Glu Glu Ala Arg Pro Ala) (SEQ ID NO: 5). Therefore, the epitope recognized by the monoclonal antibody lies within this 15 amino acid span.--

In the Figures:

Applicant proposes to amend the figures as indicated in red on the enclosed sheets of figures (**Exhibit A**). Applicant will submit formal replacement sheets upon the Examiner's acceptance of the proposed changes.

In the Claims:

Please cancel claims 38-59 without prejudice. Applicant reserves the right to pursue the subject matter of these claims in the future in a related application at Applicant's discretion.

Please add the following claims:

--60. (new) A recombinant DNA sequence encoding a human thyroid peroxidase which is secreted from a cell, wherein the DNA has a stop codon at nucleotides 2629-2631 of SEQ ID NO: 2.--

--61. (new) A recombinant DNA sequence consisting of nucleotides 1-2628 of SEQ ID NO: 2.--

--62. (new) A recombinant DNA sequence consisting of nucleotides 85-2628 of SEQ ID NO: 2.--

--63. (new) A recombinant DNA sequence encoding a human thyroid peroxidase that consists of amino acids 1 to 848 of the amino acid sequence shown in SEQ ID NO: 3.--

--64. (new) A plasmid vector designated ATCC accession number CRL 10250.--

--65. (new) A DNA encoded by the vector of claim 64.--

--66. (new) A vector which comprises the DNA sequence of claim 60.--

--67. (new) A host cell transformed with the vector of claim 66.--

Support for the Amendments:

The amendments to the paragraph beginning at page 1, line 10 address the status of the priority applications of the instant application. No new matter has been added.

The amendment to the paragraph beginning at page 12, line 17 addresses the identification of the sequence. A replacement Sequence Listing is enclosed. No new matter has been added.

The amendments to the paragraph beginning at page 12, line 22 addresses the identification of the sequence and the brief description of panels 7A to 7F in the Figures. No new matter has been added.

The amendment to the paragraph beginning at page 15, line 14 addresses the identification of the sequences. No new matter has been added.

The amendment to the paragraph beginning at page 15, line 26 addresses the identification of the sequences. No new matter has been added.

The amendments to the paragraph beginning at page 16, line 13 address the numbering of the Figures. In that regard, the Figures have now been consecutively numbered. No new matter has been added.

The amendments to the paragraph beginning at page 48, line 21 address the identification of the nucleotide sequence of the primer described therein, and identify the cDNA sequence of human thyrodine peroxidase as published in Magnusson et al., (1987). Magnusson et al. (1987) was incorporated by reference in the application at the time of filing (see page 16, lines 18-21). No new matter has been added. A Declaration under MPEP § 608.01(p) is enclosed herewith (**Exhibit B**).

The amendments to the paragraph beginning at page 69, line 2 address the identification of the sequences. No new matter has been added.

The amendment to the paragraph beginning at page 73, line 21 addresses the identification of the sequences. No new matter has been added.

The amendments to the figure numbers address the consecutive numbering of the figures. No new matter has been added. The amendment to Figure 7F corrects the typographical error of nucleotide 2516. The "G" at position 2516 should be replaced with --C--. This amendment is supported by the cDNA sequence of human thyrodine peroxidase as published by Magnusson et al. (1987) that was incorporated by reference into the present application. The published nucleotide sequence of the hTPO cDNA has been inserted into the paragraph beginning at page 48, line 21, as set forth above.

Support for claim 60 may be found in the specification at page 48, lines 29-32; and in Figures 6 and 7.

Support for claim 61 may be found in the specification at page 48, lines 29-32; and in Figure 7.

Support for claim 62 may be found in the specification at page 48, lines 29-32; page 57, lines 28-30; and in Figure 7.

Support for claim 63 may be found in the specification at page 48, lines 29-32; page 57, lines 28-30; and in Figure 7.

Support for claim 64 may be found in the specification at page 57, lines 8-11.

Support for claim 65 may be found in the specification at claim 11.

Support for claim 66 may be found in the specification at claim 14.

Support for claim 67 may be found in the specification at claim 15.

Remarks

As a preliminary matter, Applicant thanks the Examiner for the opportunity on August 9, 2001 to discuss the claims, the art, and the outstanding Office Action with Applicant's undersigned representatives. Based on that discussion, the undersigned understand that claims 60-63 submitted herewith may be allowable upon the Examiner's further review.

In addition, Applicant has added claim 64 directed to the deposited vector. Applicant has also added claim 65 directed to the DNA encoded by the vector of claim 64, and claims 66-67 directed to a vector, and host cell encoding the DNA of claim 60. Applicant respectfully submits that these claims are also patentable over the references.

As set forth above, Applicant has canceled claims 38-59, and has added claims 60-67. Accordingly, claims 60-67 are pending.

Item 3 of the Office Action - Objections to the Specification and Declaration

(i) The Examiner has objected to the Brief Description of the Drawings because the specification does not describe Figure 7, panels A-F.

Applicant has amended the specification as set forth above, and respectfully submits that the objection should be withdrawn.

(ii) The Examiner has objected to the specification because it does not reflect the status of the parent applications.

Applicant has amended the specification as set forth above, and as suggested by the Examiner. Applicant respectfully submits that the objection should be withdrawn.

(iii) The Examiner has maintained the objection to the Declaration and requirement for certified copies of the PCT applications identified in the first paragraph of the specification.

As the undersigned discussed with the Examiner, Applicant understands that proper identification of the PCT applications in the Declaration would overcome the objection. Accordingly, Applicant encloses herewith a newly signed Declaration identifying the priority applications (including the PCT applications) of the instant application (**Exhibit C**).

Item 5 of the Office Action - Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 38-46, and 48-56 under 35 USC 112, first paragraph. The Examiner states that there is allegedly no support for "antibody associated with thyroiditis".

Applicant has canceled claims 38-56. Accordingly, the rejections of claims 38-46 and 48-56 are rendered moot. Applicant respectfully traverses the rejection.

Applicant respectfully submits that new claims 60-67 do not include the phrase "antibody associated with thyroiditis", and accordingly the rejection should not be maintained with respect to the new claims.

Item 6 of the Office Action - Rejections Under 35 U.S.C. § 102

The Examiner has rejected claims 38 and claim 58 under 35 U.S.C. 102 as being anticipated by Libert et al.

Applicant has canceled claims 38 and 58 as set forth above. Accordingly, the rejections under 35 U.S.C. 102 are rendered moot.

Item 7 of the Office Action - Rejections Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 38-46, and 48-56, and 58-59 under 35 U.S.C. § 103 as allegedly obvious over Seto et al. or Libert et al. in view of Lee et al., or Ellis et al., or EP 139,417, or Rose et al., and Magnusson et al.

Applicant has canceled claims 38-59 as set forth above. Accordingly, the rejections of those claims under 35 U.S.C. § 103 are rendered moot. Applicant respectfully traverses the rejections. Applicant has added claims 60-67, which are not taught or suggested by the references as discussed herein.

The Legal Standard for Establishing Obviousness Under 35 U.S.C. § 103

To establish a prima facie case of obviousness, three basic criteria must be met (MPEP 2143).

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a primary reference or to combine reference teachings.

Second, there must be a reasonable expectation of success that the suggested combination will work.

Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure (*In re Vaeck*, 947 F.2d 488, (Fed. Cir. 1991)). Hindsight reconstruction cannot be used to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention (*In re Fine*, 837 F.2d 1071, 1075, (Fed. Cir. 1988)). Applicant respectfully submits that the Examiner has not met the burden of proof.

Applicant's Invention

As recited in the claims, Applicant's invention is directed to a recombinant DNA sequence that encodes a secretable human thyroid peroxidase that has a stop codon at nucleotides 2629 to 2631 of SEQ ID NO: 2. Applicant's claim 61 is directed to a recombinant DNA sequence consisting of nucleotides 1 to 2628 of SEQ ID NO: 2. Applicant's claim 62 is directed to a recombinant DNA sequence consisting of nucleotides 85 to 2628 of SEQ ID NO: 2. Applicant's claim 63 is directed to a DNA sequence that encodes a thyroid peroxidase consisting of amino acids 1 to 848 as shown in

SEQ ID NO: 3. Applicant's claim 64 is directed to the plasmid vector deposited with the ATCC and designated accession number CRL 10250. Applicant's claim 65 is directed to a DNA encoded by the vector of claim 64. Claims 66 and 67 are directed to a vector and host cell encoding the DNA of claim 60.

In contrast to Applicant's invention, the cited references alone or in combination do not teach or suggest a DNA sequence that encodes secreted hTPO that comprises a stop codon at nucleotides 2629 to 2631 of SEQ ID NO: 2. The references also do not teach or suggest a DNA sequence consisting of nucleotides 1 to 2628 of SEQ ID NO: 2, or nucleotides 85 to 2628 of SEQ ID NO: 2. The references also do not teach or suggest a DNA sequence encoding a hTPO that consists of amino acids 1 to 848 of the amino acid sequence shown in FIG. 7. The references also do not teach or suggest the plasmid vector as deposited with the ATCC.

A. No Motivation

None of the cited references alone or in combination provide a suggestion or motivation to obtain the DNA sequences encoding the truncated hTPO as recited in claims 60-67. The references do not explicitly or implicitly suggest which codon(s) of hTPO should be altered to produce the hTPO as claimed.

B. No Reasonable Expectation of Success

Without motivation to obtain the DNA sequences as claimed, there can be no reasonable expectation of success of obtaining the claimed invention based on the cited references.

C. All Claim Limitations are Not Disclosed by the Art

The claims require that the nucleic acid encodes a secreted hTPO that has a stop codon at nucleotides 2629 to 2631 of SEQ ID NO: 2; the nucleic acid consists of nucleotides 1 to 2628 of

SEQ ID NO: 2, or 85 to 2628 of SEQ ID NO: 2; or the nucleic acid encodes a hTPO that consists of amino acids 1-848 of the amino acid sequence shown in SEQ ID NO: 3.

None of the references alone or in combination disclose all of the claim limitations. Seto discloses a cDNA fragment consisting of 842 base pairs, and its predicted amino acid sequence. Libert discloses a cDNA sequence for the full length hTPO consisting of 3042 base pairs. The fact that the references do not disclose all the claim limitations is supported by the statement made by the Examiner in the Office Action dated January 21, 1998 (paper 12, page 9). The Examiner states that "neither Seto et al or Libert et al teach a recombinant DNA sequence encoding human thyroid peroxidase which is secreted from a cell with stop codons upstream from a transmembrane domain, a vector which comprises the DNA sequence or a host cell transformed with the vector".

As the Examiner has indicated, EP 139417 discloses that deletion of the carboxyl terminus of the gD protein of Herpes Simplex Virus results in the protein's secretion from the transfected cells. Rose discloses that deletion of the carboxy terminus of the G protein results in the protein's secretion from transformed cells. Magnusson discloses the cDNA for porcine TPO. Lee discloses expression vectors containing DHFR and MMTV promoters which are capable of expressing genes in CHO cells. Ellis discloses an SV40 based expression vector, which is capable of expressing proteins in CHO cell lines. Accordingly, none of the references, alone or in combination, disclose all the limitations as claimed.

D. Conclusion

Applicant respectfully submits that he has met the legal standard for nonobviousness because none of the cited references teach or suggest nucleic acid molecules that either have a stop codon at nucleotides 2629 to 2631 of SEQ ID NO: 2, that consist of nucleotides 1 to 2628 of SEQ ID NO: 2, or nucleotides 85 to 2628 of SEQ ID NO: 2, or encode a protein that consists of amino acids 1-848 as shown in SEQ ID NO: 3.

The primary references (Seto et al. and Libert et al.) teach a cDNA for a fragment hTPO (Seto) or a cDNA for a full length hTPO (Libert). Further, the secondary references (Lee et al., Ellis et al., EP 139,417, Rose et al., and Magnusson et al.) do not teach or suggest what the primary reference fails to teach, namely, nucleic acid molecules that either have a stop codon at nucleotides 2629 to 2631 of SEQ ID NO: 2, that consist of nucleotides 1 to 2628 of SEQ ID NO: 2, or nucleotides 85 to 2628 of SEQ ID NO: 2, or encode a protein that consists of amino acids 1-848 of hTPO. Accordingly, the combination of the primary and secondary references does not render obvious the claimed compositions.

Items 8 and 9 of the Office Action - New Grounds for Objection

(i) The Examiner has objected to the Figures and the Brief Description of the Figures because in view of the previous Amendments to the specification, neither the Figures nor the Brief Description of the Figures are in consecutive numerical order.

Applicant has amended the Figures and the Brief Description of the Figures as set forth above. Applicant respectfully submits that he has overcome the Examiner's objection.

(ii) The Examiner has objected to Figures 6, 7, 18, and 19 because neither the Figures nor the Brief Description of Figures discloses unique identifiers in the form of SEQ ID NOs for the disclosed sequences. Applicant has amended the specification as set forth above, and in particular, Applicant has provided SEQ ID NOs for the sequences disclosed in Figures 6, 7, 18, and 19, as well as for the sequences disclosed within the text of the specification. A paper and computer readable form of the amended sequence listing is enclosed herewith (**Exhibit D**). A Declaration Under 37 CFR 1.821(f) is enclosed herewith as **Exhibit E**. Applicant respectfully submits that the objection has been overcome.

Item 10 of the Office Action - Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 38-46, 48-56, and 58-59 under 35 U.S.C. § 112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Applicant has canceled claims 38-59 as set forth above. Accordingly, the rejection of those claims is rendered moot. Applicant has added claims 60-67, which do not include the phrase to which the Examiner has rejected the claims. Applicant respectfully submits that the rejection should be withdrawn.

In view of the foregoing amendments and remarks, Applicant respectfully submits that the claims are not disclosed or suggested by the prior art, and respectfully submits that the claims are in condition for allowance. Notice of which is respectfully requested.